Vaccine 33 (2015) 6967–6969

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

The ESPID/ESWI Joint Symposium—A strong vote for universal influenza vaccination in children in Europe

Robin Kobbe*

Department of Paediatrics, Infectious Diseases and Immunity, University Medical Centre Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany

ARTICLE INFO

Article history:
Available online 16 September 2015

Keywords:
Influenza
Vaccine
Children
Adverse events
Europe

ABSTRACT

During this year's 33rd annual meeting in Leipzig, Germany, the European Society of Paediatric Infectious Diseases (ESPID) jointly together with the European Scientific Working group on Influenza (ESWI), organized a staged debate on the motion of universal annual immunization of children against influenza as a cost-effective health intervention in Europe. Six invited speakers, all experts in the field of influenza vaccination, who were not necessary confident with their given position of pro or contra, battled each other with short oral presentations to convince the audience to vote for or against the motion.

Opening the floor of this ESPID/ESWI Joint Symposium, the chairman Ab Osterhaus first of all asked the audience in the crowded lecture hall to vote on the motion. Frankly speaking, most participants were either paediatricians or infectious disease specialists and supposedly because no real vaccine opponents were present, only few attendees voted against universal vaccination of all European children.

In the first presentation, Pieter Fraaij reviewed the literature on the incidence and outcome of influenza in different age groups. It became clear that there is a considerable disease burden, not only in Europe. During annual outbreaks the number of influenza infections is highest in children affecting 20–30% of the total paediatric population, mostly with even higher attack rates among selected high-risk groups [1]. Children who become ill are additionally responsible for a substantial loss of parental working days. Furthermore, although most paediatric influenza cases seen in the outpatient setting present as a self limiting respiratory disease, every season a considerable number of children need hospitalization and up to 10% of all admitted children need management on the intensive care unit (ICU) [2]. Of these ICU patients, only half have an underlying chronic predisposing condition (e.g. cystic fibrosis, asthma, or immunodeficiency), while the other half represent previously healthy children progressing to severe, sometimes life-threatening disease with complicating conditions like ARDS, encephalitis, myocarditis, secondary severe bacterial infection or other atypical conditions.

At this point a provocative thesis opened the stage for discussion: despite seasonal flu being a cause of severe disease in children, most severe cases will recover fully with oxygen, good supportive care, specific antiviral drugs and antibiotic treatment. To underline this argument, Fraaij cited a recent publication to show that even after the introduction of universal influenza vaccination in the United States, seasonal acute respiratory infection outbreaks will not disappear and that severe respiratory tract infections, including influenza, will always have to be managed [3]. Discussing this findings, the attentive listener asked him/herself if this position might be untenable, simply because respiratory syncytial virus, human metapneumovirus, adenovirus, and others are different from influenza virus and not affected by influenza vaccination. However, at the moment we only have an effective vaccine against influenza available. But as Fraaij reported that only few children die on European ICUs each year, he at the same time raised questions like "what is a tolerable number of childhood deaths due to influenza?", "how these numbers carry weigh against childhood accidents or even homicide?", and "how shall we use death rates and estimations on cost-effectiveness to bring forward an argument?". In particular paediatricians will find it difficult to talk to parents whose child has died despite best supportive ICU care due to a potential vaccine-preventable disease. Every doctor and also policy maker should consider his/her child being among the 43% of previously healthy children living in the United States who succumbed to a disease for which we have a vaccine readily available [4]. But during the second presentation, Terho Heikkinen argued that mortality is not the only reason why we should vaccinate the children and asked the audience to look at the available data in a different way. As we are unable to predict which

* Tel.: +49 040 7410 58037; fax: +49 040 7410 59646.
E-mail address: r.kobbe@uke.de

http://dx.doi.org/10.1016/j.vaccine.2015.09.018

previously healthy individual will acquire influenza and develop a severe form of disease, most European countries have run selective influenza vaccination programs aiming to directly protect populations at higher risk and to thereby reduce mortality. Among these high risk groups are pregnant woman, the elderly, people with chronic diseases, especially with pulmonary or heart diseases, and immunocompromized individuals. Studies Heikkinen et al. conducted in Finland showed that every season 16.7% of all children fell ill with laboratory confirmed influenza [5]. Certainly, as in the United States, most cases are not life threatening and the highest burden always lies within the community [6]. Some clinical presentations are widely known, as common cold, otitis media, sinusitis and pneumonia, and often resolve with or without antibiotic prescriptions. Other severe disease phenotypes were rarely seen or recognized by the single general practitioner, but contributed to hospitalization [7,8]. These studies confirmed that the youngest children are at highest risk, often being admitted to hospital with a sepsis-like syndrome [9]. Heikkinen showed age-specific incidence data and the need to protect infants by vaccination because of their immature immune system, as it has never seen influenza antigens before, whatever strain might circulate in a given year, it is always a "pandemic" [10]. Before, Fraaij used the same data to argue against spending money on universal childhood vaccination programs because immune responses against influenza vaccination in infants are poor and it had been brought forward rather to increase efforts to vaccinate their mothers to boost maternal passive immunity [11]. Of course, immunization of pregnant mothers definitely has the potential to protect their offspring against influenza. However, maternal immunoglobulin IgG has a relatively short half-life and young children continue to be at risk for vaccine-preventable diseases. Importantly, Heikkinen reported that in Finland, where the influenza vaccine has been included in the national vaccination program for children 6–35 months of age, economical studies not only showed that the intervention is cost-effective, but rather cost-saving [12]. Continuing from the economical point of view, Richard Pebody reviewed in the following minutes several studies that evaluated or modelled influenza vaccination programs. Almost all of them reported more or less good cost-effectiveness results [13,14]. But from the political point of view, he also showed critical press reports on poorer influenza vaccine effectiveness than formerly expected. He found policy makers under pressure. Moreover, he cited a Cochrane review that summarized to find no evidence of a vaccine effect on secondary cases, lower respiratory tract disease, drug prescriptions, otitis media and other consequences [15]. Pebody also pointed out that in situations of limited resources in the immunization and public health sector budget, a choice is always measured in terms of the value of best alternative foregone.

Adam Finn, the current president of ESPID, strongly promoted the idea of blocking virus transmission to those at very high-risk, including pregnant women by vaccinating the children. He presented data showing that children – because of their infectiousness – are the factories for influenza epidemics. Because they are key players, Finn argued, the inclusion of healthy children into national vaccination programs will result in reduced mortality and overall disease burden in the whole population. This indirect vaccine efficacy has been demonstrated in an elegant clinical trial of trivalent inactivated influenza vaccination controlled by hepatitis A vaccine given to children aged 3–15 years in 50 remote isolated Hutterite communities in Canada. The mass vaccination of children in the community resulted in a 61% reduction of influenza disease in the respective unvaccinated adult population [16]. Finn reminded us that this study only confirmed previous epidemiological data from the United States and Japan showing that universal vaccination programs indeed reduced excess deaths due to pneumonia and influenza in the respective populations [17]. The highly accepted new intranasal live attenuated influenza vaccine (LAIV), due to safety issues only licenced in children over two years of age, is highly efficacious with a higher protective efficacy than inactivated influenza vaccines [18]. High coverage of US school-based LAIV programs showed an effect of indirect protection in intervention households [19,20]. Interestingly, Finn also presented recent implementational studies of school-based LAIV programs in the United Kingdom and was optimistic to achieve coverage levels >50% that might result in an indirect effect by reducing influenza in unvaccinated children. Unfortunately, measuring hypothetical cost-savings of hypothetical respective positive indirect effects of mass vaccination appears to be difficult.

Finally, Miriam Sturkenboom and Timo Vesikari focused on adverse events and side effects. In the last two presentations they first described studies, reports and registry data of unwanted pro-inflammatory responses and discussed the evidence of causal relation of these with administration of influenza vaccines. ASIA, an acronym for autoimmune/inflammatory syndrome induced by adjuvants, also called Shoenfeld's syndrome, stands for a clinical and immunological spectrum of non-specific and specific manifestations of autoimmune disease, mainly associated with the adjuvants squalene and aluminium hydroxide [21]. Both adjuvants, which were designed to enhance specific antibody production, were accused to activate the immune system in a negative way by releasing inflammatory cytokines that trigger manifestations of autoimmunity or autoimmune disease. All licensed inactivated influenza vaccines contain aluminium adjuvants and one contains squalene to spare vaccine doses and induce adequate immune response and protection in young children and the elderly. Vesikari clearly stated that the acceptance of ASIA as a real health risk would invalidate influenza vaccination programs as a whole, especially if wide segments of population are being vaccinated on an annual basis. Nevertheless, supporters of ASIA continue to relate various forms of systemic vasculitis (e.g. leukocytoclastic vasculitis, giant cell arteritis), SLE, rheumatoid arthritis, inflammatory myopathy and Guillain–Barré syndrome with influenza vaccination. This unfair, non-scientific way of undermining vaccination programs by sprouting a theoretical risk is quite common yet causality is almost impossible to prove, as the number of affected patients is small. This is different for narcolepsy, a chronic debilitating sleep disorder caused by hypothalamic hypocretin deficiency. A sharp and significant increase in the number of newly diagnosed narcolepsy cases among children and adolescents has been notified during the H1N1 influenza pandemic in 2009–2010 in Finland [22]. During the pandemic, adjuvanted vaccines were used at a large scale resulting in a huge safety experiment at the population level. Subsequently, an increased risk of narcolepsy only in persons under 40 years of age vaccinated with Pandemix® was confirmed by the Swedish registry study while there was no significant association with any other disease [23]. This registry collected follow-up data of 5.8 million people (3.3 million vaccinated, 2.5 million not vaccinated) over 2.2 years. In addition, retrospective analysis from narcolepsy incidence data in the United Kingdom also confirmed the signal for vaccination with Pandemrix® at any time before onset of the disease [24]. Surprisingly, narcolepsy was associated only with the use of the AS03-adjuvanted Pandemrix® vaccine, but not seen in association with another AS03-adjuvanted influenza vaccine (Arepanrix®), neither in connection with a squalene only (MF59) adjuvanted influenza vaccine nor with unadjuvanted seasonal influenza vaccine (Fluarix®), which was produced in the same way as Pandemrix®. Vesikari urged to take the association seriously, as it has been suggested that the combination of squalene and α-tocopherolin was too much of a too strong adjuvant (AS03) for an age group that did not actually need it. A recent investigation of the production process of the "split" influenza vaccine Pandemrix showed the formation of high quantity of the strongly immunogenic polymerized form of influenza nucleoprotein antigen NP,

not present in Arepanrix®. Especially in combination with a highly susceptible genetic disposition (HLA-DBQ-1*602), this could have resulted in an inherently strong response and autoimmunity, supported by the observation that NP is recognized by antibodies from children with narcolepsy [25]. Vesikari suggested as one option for future universal vaccination programs to avoid needless high potent adjuvants in persons with a strong immune response, as they could potentially trigger an autoimmune reaction.

In contrast, Miriam Sturkenboom emphasized that after the initial safety signal around Pandemrix® became public active surveillance programs focused only on conditions of special interest. In her presentation, she first used the example of Guillain–Barré Syndrome (GBS) to point out that in these studies potential detection bias has not been properly addressed and that data might also suffer from ascertainment bias [26,27]. Combining these effects may well explain the observed associations, as shown by simulation studies. This might be even more true when follow-up time is short, diagnostic lag times of these rare, formerly underdiagnosed diseases were decreased, and finally when victim compensation is initiated. For the case of narcolepsy, although the signalling countries did their best to quantify adverse events, they conducted these rapid risk assessment studies in the midst of the public awareness. Therefore, most studies were not powered enough and media effects were not properly excluded so that methodically, it could not be distinguished between a vaccine and an awareness effect [28]. Sturkenboom summarized that in her opinion, as long as there is no evidence-based explanation for the biological mechanisms of Pandemrix® causing narcolepsy, we should not immediately discard potentially useful adjuvants.

In summary, participants of the ESPID/ESWI Joint Symposium – based on scientific evidence and meticulous diligence – strongly support universal annual immunization of all children against influenza as a cost-effective health intervention in Europe. For Germany, host country of this year's ESPID annual meeting, recently published epidemiological and health economic simulation data show that national LAIV immunization of all children would lead to a substantial reduction in influenza-associated disease at a reasonable cost [29,30].

Conflict of interest statement

The author is a member of ESPID and was invited by ESWI to participate in the Joint Symposium in Leipzig free of charge. He has no other conflict to declare.

References

[1] Fraaij PL, Heikkinen T. Seasonal influenza: the burden of disease in children. Vaccine 2011;29(October):7524–8.
[2] Fraaij PL, Bodewes R, Osterhaus AD, Rimmelzwaan GF. The ins and outs of universal childhood influenza vaccination. Future Microbiol 2011;6(10):1171–84.
[3] Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al., CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015;372(February (9)):835–45.
[4] Wong KK, Jain S, Blanton L, Dhara R, Brammer L, Fry AM, et al. Influenza-associated pediatric deaths in the United States, 2004–2012. Pediatrics 2013;132(November (5)):796–804.
[5] Heikkinen T, Silvennoinen H, Peltola V, Ziegler T, Vainionpaa R, Vuorinen T, et al. Burden of influenza in children in the community. J Infect Dis 2004;90(October (8)):1369–73.
[6] Poehling KA, Edwards KM, Weinberg GA, Szilagyi P, Staat MA, Iwane MK, et al., New Vaccine Surveillance Network. The underrecognized burden of influenza in young children. N Engl J Med 2006;355(July (1)):31–40.
[7] Silvennoinen H, Peltola V, Vainionpää R, Ruuskanen O, Heikkinen T. Incidence of influenza-related hospitalizations in different age groups of children in Finland: a 16-year study. Pediatr Infect Dis J 2011;30(2):e24–8.
[8] Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med 2000;342(January (4)):232–9.
[9] Silvennoinen H, Peltola V, Vainionpää R, Ruuskanen O, Heikkinen T. Admission diagnoses of children 0–16 years of age hospitalized with influenza. Eur J Clin Microbiol Infect Dis 2012;31(3):225–31.
[10] Bodewes R, Fraaij PL, Osterhaus AD, Rimmelzwaan GF. Pediatric influenza vaccination: understanding the T-cell response. Expert Rev Vaccines 2012;11(8):963–71.
[11] Madhi SA, Cutland CL, Kuwanda L, Weinberg A, Hugo A, Jones S, et al., Maternal Flu Trial (Matflu) Team. Influenza vaccination of pregnant women and protection of their infants. N Engl J Med 2014;371(September (10)):918–31.
[12] Salo H, Kilpi T, Sintonen H, Linna M, Peltola V, Heikkinen T. Cost-effectiveness of influenza vaccination of healthy children. Vaccine 2006;24(June (23)):4934–41.
[13] Ott JJ, Klein Breteler J, Tam JS, Hutubessy RC, Jit M, de Boer MR. Influenza vaccines in low and middle income countries: a systematic review of economic evaluations. Hum Vaccin Immunother 2013;9(7):1500–11.
[14] Jit M, Newall AT, Beutels P. Key issues for estimating the impact and cost-effectiveness of seasonal influenza vaccination strategies. Hum Vaccin Immunother 2013;9(4):834–40.
[15] Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. Cochrane Database Syst Rev 2012;8:CD004879.
[16] Loeb M, Russell ML, Moss L, Fonseca K, Fox J, Earn DJ, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA 2010;303(March (10)):943–50.
[17] Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. N Engl J Med 2001;344(March (12)):889–96.
[18] Ambrose CS, Wu X, Knuf M, Wutzler P. The efficacy of intranasal live attenuated influenza vaccine in children 2 through 17 years of age: a meta analysis of 8 randomized controlled studies. Vaccine 2012;30(January (5)):886–92.
[19] Glezen WP, Gaglani MJ, Kozinetz CA, Piedra PA. Direct and indirect effectiveness of influenza vaccination delivered to children at school preceding an epidemic caused by 3 new influenza virus variants. J Infect Dis 2010;202(December (11)):1626–33.
[20] King Jr JC, Stoddard JJ, Gaglani MJ, Moore KA, Magder L, McClure E, et al. Effectiveness of school-based influenza vaccination. N Engl J Med 2006;355(December (24)):2523–32.
[21] Vera-Lastra O, Medina G, Cruz-Dominguez Mdel P, Jara LJ, Shoenfeld Y. Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome): clinical and immunological spectrum. Expert Rev Clin Immunol 2013;9(4):361–73.
[22] Partinen M, Saarenpää-Heikkilä O, Ilveskoski I, Hublin C, Linna M, Olsén P, et al. Increased incidence and clinical picture of childhood narcolepsy following the 2009 H1N1 pandemic vaccination campaign in Finland. PLoS ONE 2012;7(3):e33723.
[23] Persson I, Granath F, Askling J, Ludvigsson JF, Olsson T, Feltelius N. Risks of neurological and immune-related diseases, including narcolepsy, after vaccination with Pandemrix: a population- and registry-based cohort study with over 2 years of follow-up. J Intern Med 2014;275(2):172–90.
[24] Miller E, Andrews N, Stellitano L, Stowe J, Winstone AM, Shneerson J, et al. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009 influenza vaccine: retrospective analysis. BMJ 2013;346(February):f794.
[25] Vaarala O, Vuorela A, Partinen M, Baumann M, Freitag TL, Meri S, et al. Antigenic differences between AS03 adjuvanted Influenza A(H1N1) pandemic vaccines: implications for Pandemrix-associated narcolepsy risk. PLoS ONE 2014;9(12):e114361.
[26] Dodd CN, Romio SA, Black S, Vellozzi C, Andrews N, Sturkenboom M, et al., Global H1N1 GBS Consortium. International collaboration to assess the risk of Guillain Barré Syndrome following Influenza A(H1N1) 2009 monovalent vaccines. Vaccine 2013;31(September (40)):4448–58.
[27] Romio S, Weibel D, Dieleman JP, Olberg HK, de Vries CS, Sammon C, et al. Guillain–Barré syndrome and adjuvanted pandemic Influenza A(H1N1) 2009 vaccines: a multinational self-controlled case series in Europe. PLoS ONE 2014;9(1):e82222.
[28] Sturkenboom MC. The narcolepsy-pandemic influenza story: can the truth ever be unraveled? Vaccine 2015;33(January (Suppl 2)):B6–13.
[29] Damm O, Eichner M, Rose MA, Knuf M, Wutzler P, Liese JG, et al. Public health impact and cost-effectiveness of intranasal live attenuated influenza vaccination of children in Germany. Eur J Health Econ 2015;16(June (5)):471–88.
[30] Heikkinen T, Tsolia M, Finn A. Vaccination of healthy children against seasonal influenza: a European perspective. Pediatr Infect Dis J 2013;32(8):881–8.